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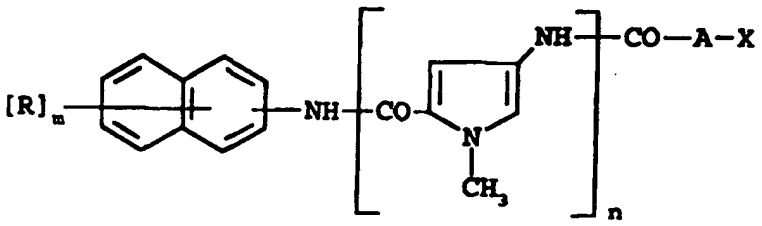
(54) Title: INCREASED BIOAVAILABILITY OF BIOLOGICALLY ACTIVE COMPOUNDS BY LINKING TO POLYPYRROLECARBOXAMIDONAPHTHALENE DERIVATIVES

(57) Abstract

A compound of formula (II) wherein R is an acidic group; m is an integer of 1 to 3; n is zero or an integer of 1 to 3; A is an enzymatically hydrolyzable spacer; and X is a biologically active compound; or a pharmaceutically acceptable salt thereof, for use as an antiproliferative, in particular anti-tumor and anti-angiogenic agent, and anti-inflammatory agent, is provided.



(II)

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Increased bioavailability of biologically active compounds by linking to Polypyrrolecarboxamidonaphthalene derivatives

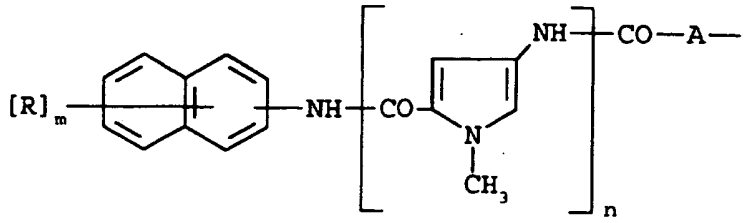
The present invention relates to a method for improving systemic bioavailability of a biologically active compound, to poly-pyrrolecarboxamidonaphthalenic acid derivatives, a process for their preparation, a pharmaceutical composition containing them and their use in therapy.

The therapeutic efficacy of all drugs is strongly influenced by different parameters that can affect their bioavailability.

For instance, in the case of some very promising cytotoxic agents, such as Paclitaxel®, known also as taxol and camptothecin analogs, the extremely low solubility in water compels the clinicians to use excipients like ethanol and Cremofor® endowed with a substantial toxicity and to adopt very long infusion time. Therefore there is the need in therapy of a system able to dissolve this kind of molecules in aqueous media and in particular in physiological conditions and/or to release slowly the drug in the active form, without reaching immediately the peak and usually a toxic concentration.

Moreover, a strong protein binding could also protect active substances from metabolic inactivation and fast excretion.

The present invention therefore concerns, as a first object, a process for improving systemic bioavailability of a biologically active compound X, the method comprising providing such active compound X bound to a carrier group having the following formula (I)



(I)

wherein

R is an acidic group;

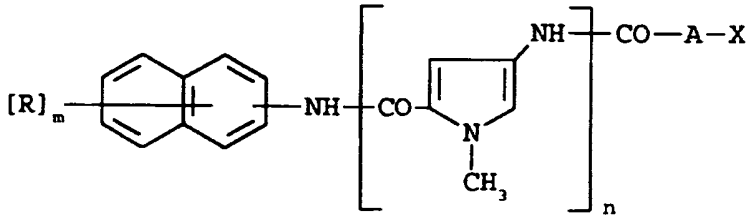
m is an integer of 1 to 3;

n is zero or an integer of 1 to 3;

A is an enzymatically hydrolyzable spacer;

or a pharmaceutically acceptable salt thereof.

A further object of the present invention is a new compound of formula (II)



(II)

wherein

R, X, m, n, and A are as defined above, and the pharmaceutically acceptable salts thereof.

Object of the invention is also to provide a pharmaceutical composition containing at least a compound of formula (II) or a pharmaceutically acceptable salt thereof, as defined above, as a therapeutically active agent, and a pharmaceutically acceptable carrier and/or diluent.

A biologically active compound X in a compound of formula (I) or (II) can for instance be a compound selected from a taxane compound, a camptothecin compound, an epipodophyllotoxin compound, an anthracycline compound, a distamycin compound, a

ceramide compound, benzoylcarbinol, tetrahydro S and hydrocortisone; or a pharmaceutically acceptable salt thereof.

When in a compound (I) or (II) two or more acidic groups are present on the naphthalene moiety, they may be the same or different, preferably the same, for instance chosen from the group including sulfonic, carboxylic and phosphonic acids.

The R substituent(s) may be on either or both the aryl moieties of the naphthalene ring.

An enzymatically hydrolyzable spacer A in a compound of formula (I) or (II) can be for instance:

a) a group -Y-CO-, wherein Y is a C_1-C_6 alkylene or C_2-C_6 alkenylene chain, a bivalent C_3-C_5 cycloalkyl or phenylene group; or

b) an amino acid residue or a peptide spacer preferably selected from βAla, Gly, Phe-Gly, Phe-Phe-, Leu-Gly, Val-Ala, Phe-Ala, Leu-Phe, Leu-Ala, Phe-Leu-Gly, Phe-Phe-Leu, Leu-Leu-Gly, Phe-Tyr-Ala, Phe-Gly-Phe, Phe-Phe-Gly, Phe-Leu-Gly-Phe, Gly-Phe-Leu-Gly-Phe, Gly-βAla, Phe-Gly-βAla, Phe-Phe-βAla, Leu-Gly-βAla, Val-Ala-βAla, Phe-Ala-βAla, Leu-Phe-βAla, Leu-Gly-βAla, Phe-Leu-Gly-βAla, Phe-Phe-Leu-βAla, Leu-Leu-Gly-βAla, Phe-Tyr-Ala-βAla, Phe-Gly-Phe, Phe-Phe-Gly-βAla, Phe-Leu-Gly-Phe-βAla, Gly-Phe-Leu-Gly-Phe-βAla, aminocaproyl.

For instance in the case of βAla the spacer is a group -HN-CH_2-CH_2-CO- and in the case of glycine the spacer is a group -HN-CH_2-CO-.

According to the definition given above for compound X, it is apparent that in said compound at least one amino or hydroxy group capable of being acylated by an acyl group of the spacer A is present; thus providing the group -NH-CO-A-X occurring in formula (II) as herein defined.

A taxane compound is for instance taxol, 7-epitaxol, taxotere or 7-epitaxotere.

A camptothecin compound is for instance camptothecin or 9-amino-camptothecin.

An epipodophyllotoxin compound is for instance etoposide.

An anthracycline compound is for instance doxorubicin, epirubicin, idarubicin, 4'-iododoxorubicin, methoxymorpholino-doxorubicin and daunorubicin.

A distamycin compound is for instance tallimustine-amidoxime, i.e. 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido)pyrrole-2-carboxamido) pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime.

A ceramide compound is for instance a C_2-C_{30} ceramide compound, i.e. a N-(C_2-C_{30})-acyl-D-sphingosine, in particular C_{14}-ceramide i.e. (2S-3R-4E)-1,3-dihydroxy-2-tetradecanoyl-amido-4-octadecene.

An alkylene or alkenylene chain can be a straight or branched chain.

A C_1-C_6 alkylene chain is preferably a C_1-C_4 alkyl chain, typically $-CH_2-$, $-CH_2-CH_2-$ and $-CH_2-CH_2-CH_2-$, in particular $-CH_2-CH_2-$.

A C_2-C_6 alkenylene chain is preferably a C_2-C_6 alkenylene chain, typically -CH=CH- or $-CH=CH_2-CH_2-$, in particular cis- or trans-CH=CH-.

A bivalent C_3-C_5 cycloalkyl group is typically a cyclopropyl ring.

A as a bivalent phenylene group is typically a 1,2-phenylene group.

The invention includes within its scope also the pharmaceutically acceptable salts of the compounds of formula (II).

Examples of pharmaceutically acceptable salts of a compound of

formula (I) or (II) are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, N-methyl-glucamine, triethylamine, triethanolamine, dibenzylamine, methylbenzyl-amine, di-(2-ethyl-hexyl)-amine, piperidine, N-ethylpiperidine, N,N-diethylaminoethylamine, N-ethylmorpholine, β-phenethyl-amine, N-benzyl-β-phenethylamine, N-benzyl-N,N-dimethyl-amine and the other acceptable organic amines.

The formula reported above for the compounds (II) according to the present invention includes all the possible isomers, in particular stereoisomers, typically diastereoisomers, as well as their mixtures.

The invention includes within its scope the metabolites and the metabolic precursors or bio-precursors (otherwise known as pro-drugs) of the compounds of formula (II).

Namely the invention includes compounds which have a different formula to formula (II) above but which nevertheless upon administration to a human being are converted directly or indirectly <u>in vivo</u> into a compound of formula (II).

Preferred compounds according to the present invention are the compounds of formula (II), wherein

R is a sulfonic acid;

m is 2 or 3;

n is 1 or 2;

A is a group -Y'-CO-, wherein Y' is selected from $-CH_2-CH_2-$, -CH=CH-, and a cyclopropyl or 1,2-phenylene group; or an aminoacid residue or peptide spacer selected from β-Ala, Gly, Leu-Gly and Phe-Leu-Gly;

X is a compound selected from taxol, 7-epitaxol, epirubicin, taxotere, tallimustine-amidoxime, N-(C_2-C_{30})-acyl-D-

sphingosine, camptothecin, 9-amino-camptothecin, etoposide, doxorubicin, methoxy-morpholino-doxorubicin, benzoyl-carbinol, tetrahydro S and hydrocortisone, and the pharmaceutically acceptable salts thereof.

Specific examples of preferred compounds of formula (II) according to the invention are:

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-2'(7-epi)taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-2'(7-epi)taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-2'-taxotere;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-2'-taxotere;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-3'-etoposide;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-3'-etoposide;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-3'-doxorubicin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-3'-doxorubicin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-21-tetrahydro S;

N-(4-carbonylamino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-21-hydrocortisone;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-propionyl-2'-taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid)))-propionyl-2'-taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-propionyl-2'-taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-propionyl-2'-(7 epi)taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-propionyl-2'-(7 epi)taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-propionyl-2'-taxotere;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-propionyl-2'-taxotere;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-propionyl-20-camptothecin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalen-trisulfonic acid)))-propionyl-20-(9 amino)camptothecin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalen-disulfonic acid)))-propionyl-3'-etoposide;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalen-trisulfonic acid)))-propionyl-14-(3'-methoxymorpholino)-doxorubicin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalen-disulfonic acid)))-propionyl-1-benzoyl carbinol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalen-trisulfonic acid)))-propionyl-21-hydrocortisone;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid))β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid))β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-

naphthalentrisulfonic acid))β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl-2'-taxol;

3-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl-2-pyrrolecarbonyl-(7-imino-1,3-naphthalendisulfonic acid)))propionyl-3'-N-daunorubicin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino,1,7-naphthalendisulfonic acid)))-β-alanyl-20-O-camptothecin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino,1,7-naphthalendisulfonic acid)))-phenylalanyl-leucyl-glycyl-20-O-camptothecin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl-O-benzoylcarbinol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl-β-alanyl-O-benzoylcarbinol;

21-(N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl) hydrocortisone;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl)-O-tallimustine amidoxime;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-acetylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-exanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-acetylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-exanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene;

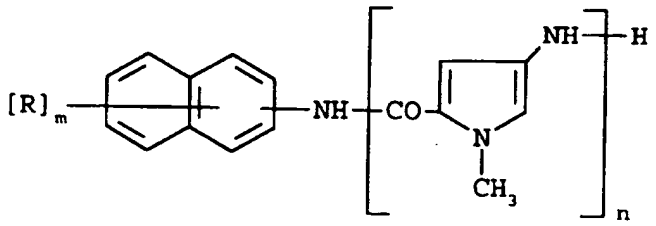
and the pharmaceutically acceptable salts thereof, in particular the sodium salts.

The binding of a carrier group of formula (I), as defined above, to a biologically active compound X, as defined above, thus providing a compound of formula (II) can be obtained for

instance by anyone of the process-variants herebelow described for the preparation of a compound of formula (II) according to the present invention.

The compounds of formula (II) of the invention and the salts thereof can be obtained for instance by a process comprising:

a) reacting a compound of formula (III)



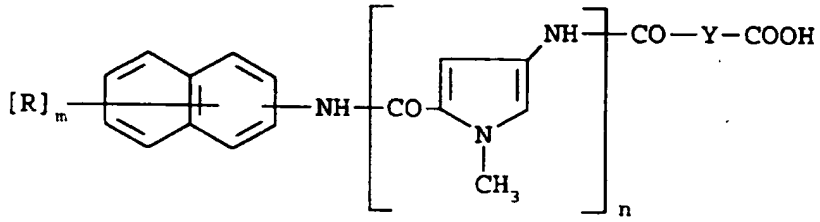
(III)

wherein R, m and n are as defined above, with a compound of formula (IV), or a derivative thereof

X-CO-Y-COOH (IV)

wherein X is as defined above and Y is a C_1-C_6 alkylene or C_2-C_6 alkenylene chain, a bivalent C_3-C_5 cycloalkyl or phenylene group, thus obtaining a compound of formula (II) wherein A is a group -Y-CO- as herein defined; or

b) reacting a compound of formula (V), or a reactive derivative thereof



(V)

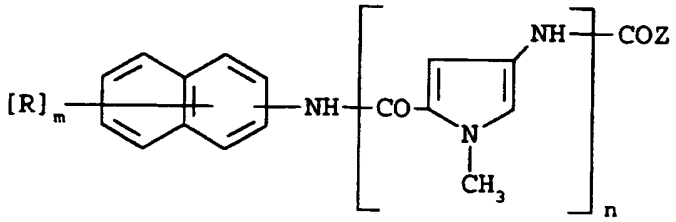
wherein R, Y, m and n are as defined above, with a compound of formula (VI)

X (VI)

wherein X is as herein defined, thus obtaining a compound of formula (II) wherein A is a group -Y-CO- as defined above;

or

c) reacting a compound of formula (VII)



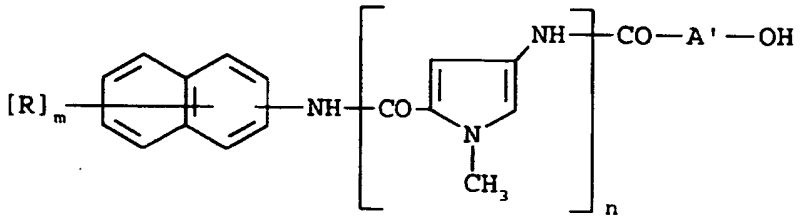
(VII)

wherein R, m and n are as defined above and Z is a leaving group, with a compound of formula (VIII)

X-A'H (VIII)

wherein X is as defined above and A' is as A an aminoacid residue or a peptidic spacer, thus obtaining a compound of formula (II), wherein A is an aminoacid residue or a peptide spacer; or

d) reacting a compound of formula (IX)



(IX)

wherein R, m and n are as defined above and A' is as A an aminoacid residue or a peptidic spacer, or a reactive derivative thereof, with a compound of formula (VI)

X (VI)

as defined above, thus obtaining a compound of formula (II), wherein A is an aminoacid residue or a peptide spacer; and, if desired, salifying a compound of formula (II); and/or, if desired, making free a compound of formula (II) from a salt thereof; and/or, if desired, separating an isomer of a compound of formula (II) from a mixture thereof.

A reactive derivative of a compound of formulae (IV), (V) and (IX) may be, for instance, an acyl isourea e.g. obtained in situ by reaction, for instance, with dicyclohexylcarbodiimide; or a mixed anhydride, obtained according to known methods, e.g. with a suitable lower alkyl, typically C_1-C_4 alkyl, haloformiate; or an imidazolide derivative obtained by reaction with carbonyldiimidazole.

A leaving group Z in a compound of formula (VII) can be for instance a 1-N-imidazolyl group.

The acylation reactions concerning process-variants a), b), c) and d) are analogy processes that can be carried out according to well known methods in the art. Similarly, salification of a compound of formula (II), making free a compound of formula (II) from a salt thereof and separating an isomer of a compound of formula (II) from a mixture thereof can be carried out according to known procedures.

Processes a) and c) are acylation reactions of amino-compounds, whereas processes b) and d) are acylation reactions of [illegible] hydroxy- and amino-compounds.

Typically, acylation of an amino group according to pr[illegible] a), b), c) and d) can be carried out at a temperature [illegible] from about 10 to about 100°C, in an organic, aprotic [illegible] chosen for instance from dimethylformamide, dimethylsu[illegible] and dimethylacetamide, if necessary in the presence [illegible] organic base, such as 4-dimethylaminopyridine, triethy[illegible] dimethylaniline or pyridine.

Typically, acylation of a hydroxy group according to pr[illegible] b) and d) can be performed at temperatures ranging from a[illegible] to about 110°C, in an organic solvent, e.g. dimethylforma[illegible], dimethylsulphoxide or dimethylacetamide, if necessary in the presence of an organic base, e.g. triethylamine, 4-

dimethylaminopyridine, pyridine or dimethylaniline.

When in the compounds of formulae (IV), (VI), (VIII), (IX) and (X) groups are present which may interfere with the reaction, they may be protected before the reaction takes place and then deprotected at the end of the reaction. For instance hydroxy, amino and/or carboxy groups may be protected and then deprotected according to common techniques known from the peptide chemistry.

A compound of formula (III), wherein n is 1, 2 or 3, is either known from WO 91/10649 or can be obtained according to a method therein described. The compounds of formula (III), wherein n is zero, are either known in the art or can be obtained according to well known procedures and in general are commercially available products.

A compound of formula (IV) can be obtained by reacting a compound of formula (VI), as herein defined, with a suitable acylating agent, e.g. are anhydride, typically succinic anhydride, phthalic anhydride, or a suitable dicarboxylic acid activated at only one carboxy group, e.g. malonic acid or maleic acid.

A compound of formula (V) can be obtained by reacting a compound of formula (III), as herein defined, with a suitable acylating agent, e.g. one of those mentioned above as to acylation of a compound of formula (VI) for obtaining a compound of formula (IV).

A compound of formula (V) wherein Z, for instance, is 1-N-imidazolyl can be obtained by reacting a compound of formula (III) with carbonylimidazole, according to known methods.

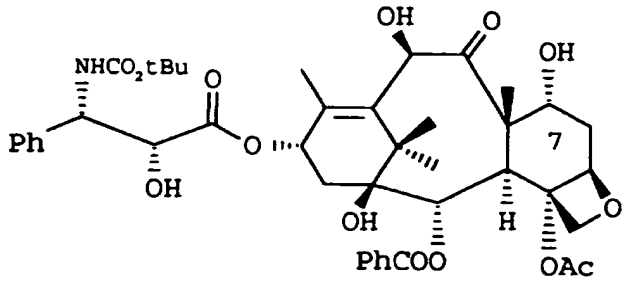
A compound of formula (VIII) or (IX), respectively, can be obtained by reacting a compound of formula (VI) or (III), respectively, with a suitable activated aminoacid or peptide, according to methods known from peptide chemistry. An activated

aminoacid or peptide can be obtained according to procedures known from the peptide chemistry.

The compounds of formula (VI) are well known in the art, for instance taxane compounds, are disclosed in JACS 93, 2325 (1971) and Proc. Am. Assoc. Cancer. Res. 31, p. 417 (1990).

7-epi-taxol is known from Tetrahedron Letters 34, 6845 (1993). Taxotere is disclosed in US 4,814,470.

7-epi-taxotere is a taxotere derivative i.e. the compound benzenepropanoic acid, .beta.-[[(1,1-dimethylethoxy)carbonyl] amino]-.alpha.-hydroxy-, 12β-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12β-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2a.alpha., 4.alpha.,4a.beta.,6.beta., 9.alpha.(.alpha.R*,.beta.S*), 11.alpha.,12.alpha.,12a.alpha., 12b.alpha.]]-, having the following chemical formula



(X)

wherein

t.Bu means t.butyl;

Ac. means acetyl and

Ph means phenyl.

A compound of formula (X) can be obtained by refluxing taxotere in an organic aprotic solvent, e.g. toluene, benzene or xylene, in the presence of a basic agent, e.g. diazabicycloundecene or Na_2CO_3, for a reaction time ranging from about 6 to about 9 hours.

Camptothecin is known from J.A.C.S. 88, 3888-3890 (1967).

9-Aminocamptothecin is disclosed by J. Med. Chem. 36, 2689-2700 (1993).

Etoposide is disclosed, for instance, by US 4,564,675.

Doxorubicin is disclosed, e.g., by Tetrahedron Letters, 1007 (1969).

Daunorubicin is disclosed, e.g., by Nature 201, 706 (1964).

Epirubicin is disclosed, e.g., by J. Med. Chem. 18, 703 (1975).

Idarubicin is disclosed, e.g., by Investigational New Drugs 4, 85 (1986).

4'-iododoxorubicin is disclosed, e.g., by Cancer Research 47, 4001 (1987).

Methoxymorpholino-doxorubicin is known from US 4,672,057.

Benzoylcarbinol is known from DE 4,203,116.

Tetrahydro S is the commercially available compound, 3α, 5β-tetrahydro-aldosterone, also known as tetrahydrocortisol.

Hydrocortisone is disclosed, e.g., by J.A.C.S. 72, 5793 (19[illegible].

The compounds of formula (II) and the pharmaceutically acceptable salts are herein also defined as the "compounds of the invention" and as the "active principle" according to the invention.

PHARMACOLOGY

The poly-pyrrolecarboxamidonaphthalenic acid derivatives formula (II), according to the present invention, have [illegible] valuable biological properties than the related X compounds, as defined above. Indeed the compounds of the invention have in general higher systemic biological activity than the related X compounds present in their chemical structure. Moreover the acidic poly-pyrrolecarboxamido-naphthalenic structure present in the compounds of the invention provides such new compounds with better solubility in physiologically acceptable solvents,

e.g. sterile water or Cremophor EL®, than the related X compounds.

Indeed it is known that X compounds, such as taxol and camptothecin, are practically insoluble in water, on the contrary, for instance, taxol-containing compounds and camptothecin-containing compounds of the invention, e.g. FCE 29142, FCE 28284 and FCE 28855, are soluble in water.

Therefore, under physiological conditions the compounds of the invention have the advantage, over the related X compounds, of providing a better therapeutic tool.

The new compounds having formula (II) and the salts thereof are useful as antiproliferative agents, in particular as antitumor and anti-angiogenic agents, and as anti-inflammatory agents.

Accordingly they can be used in a treatment to ameliorate cancer. In particular they may be administered to improve the conditions of a patient having a leukaemia such as myeloblastic leukaemia, lymphoma, sarcoma, neuroblastoma, Wilm's tumor or malignant neoplasm of the bladder, breast, lung, thyroid, colon, prostate, skin, brain, liver or ovary.

The following Examples A, B, C and D show the biological activity test data obtained for some representative compounds of the invention in comparison with the activity data obtained for reference compounds.

The chemical names of all the FCE compounds occurring in the following tables are given in the chemical experimental part of this description.

Example A

In-vitro drug cytotoxicity assays

Exponentially growing 2 x 10^4/ml B16-F10 murine melanoma cells and 1 x 10^5/ml L1210 murine leukemia cells were seeded in RPMI

1640 medium supplemented with 10 % heat-inactivated fetal calf serum and 2 mM glutamine in 24 well-plates (Costar). Scalar concentrations of tested compounds, i.e. Taxol or FCE compounds were added immediately after seeding. The inhibition of cell growth was evaluated by counting cells with a coulter counter after 72 hours incubation. For each tested compound concentration triplicate cultures were used. The anti-proliferative activity of the tested compounds was calculated from dose-response curves and expressed as IC_{50} (dose causing 50% inhibition cell growth in treated cultures relative to untreated controls). The results are shown in the following Table I.

TABLE I

IN-VITRO CYTOTOXIC ACTIVITY

FCE*	m	n	A	Cytotoxicity IC_{50} (nM)**
X = TAXOL				
28284	2	2	βala-2'	5 ± 1[1)]
28403	2	2	propionyl-2'	19 ± 9[1)]
28721	3	2	βala-2'	6 ± 1[1)]
28722	3	2	propionyl-2'	8 ± 1[1)]
28745	2	1	βala-2'	6 ± 0[1)]
28746	3	1	βala-2'	4 ± 1[1)]
28842	3	1	βala-2'	17 ± 4[1)]
29142	3	1	Phe-Leu-Gly-2'	5 ± 0.2[1)]
reference compound: taxol				35 ± 3[1)]
X = CAMPTOTHECIN				
28855	3	2	βala	11 ± 1[2)]
reference compound: camptothecin				15 ± 3[2)]

* all compounds with $R=SO_3H$

** [1)] B16-F10 murine melanoma cells 72 h treatment

[2)] L1210 murine leukemia cells 72 h treatment

Example B

In-vivo activity Taxol, FCE 29142, FCE 28721 and FCE 28746

Aim of these experiments was to compare the solubility in a biologically acceptable solvent and the activity of taxol, FCE 29142, FCE 28721 and FCE 28746. For this purpose the murine lung carcinoma M109 was chosen, since previous preclinical data had shown a good activity of taxol on this model.

Materials and Methods

Mice

BALB/c female mice were obtained from Charles River Italy. Animals were 8 to 10 weeks old at the beginning of the experiments.

Drugs

Because of its limited aqueous solubility, taxol was dissolved in a vehicle consisting of polyoxyethylated castor oil (Cremophor EL®) 50% and ethanol 50%, then diluted with a glucose 5% solution at the desired concentration. The solution was slightly hazy and precipitates formation was observed after short time.

On the contrary, FCE 29142, FCE 28721 and FCE 28746 were easily dissolved in Cremophor® + ethanol and the resulting solutions were clear for long time (more than 2 hours).

Tumor

M 109 murine carcinoma was maintained in vivo by i.m. serial transplantation. For experiments, 5 x 10^5 cells were injected i.m. in BALB/c mice.

Survival time of mice was calculated and activity was expressed in terms of T/C%.

$$T/C\% = \frac{\text{median survival time treated group}}{\text{median survival time untreated group}} \times 100$$

T.I.%= Inhibition of tumor growth % respect to controls.

TOX = Number of mice which died for toxicity.

Tox determination was made when mice died before the control or when significant body weight loss and/or spleen and/or liver size reduction were observed.

Drugs administration

Against M109 taxol, FCE 29142, FCE 28721 and FCE 28746 were administered i.v. at day 1,5,9. The obtained results are shown in Table II.

TABLE II

IN-VIVO ACTIVITY

FCE	M109 im			
	mg/Kg 1,5,9 iv	TI %	T/C %	Tox
28721	28 42 62	64 92 100	99 108 >200	0/10 0/8 0/8
28746	58 70	96 100	139 177	0/8 0/8
29142	67	100	>200	0/8
Taxol	33	98	156	0/10

Table II shows that the FCE compounds present an increased activity in terms of survival time in comparison with taxol, without any increased toxicity.

Example C

Activity on endothelial cells of ceramide-derivatives

Proliferation assay

Bovine Aortic Endothelial Cells (BAEC) were grown in DMEM added with 10% FCS and used for the assays untill the 20th *in vitro* passage. 24 h after cell seeding, the cells were treated with the test compounds for 48 h. At the end of the experiment, cell viability was determined using MTT assay.

Cell motility assay

As described by Mc Carthy et all (J.Cell Biol. 1986, 102:179-188), chemotaxis was assayed using modified Boyden Chamber with 8 µm pore size polycarbonated filters, covered with gelatin (100 µg/ml in 0.1% acetic acid). Exponentially growing cells were detached and kept 1 h at 37°C in serum containing medium before the assay. The upper chamber was filled with 5 x 10^4 cells in DMEM plus 1% FCS. The 10x concentrated 24 h medium conditioned by A375/M human melanoma cell line was added to the lower chamber with or without the test compounds. After 4 h incubation at 37°C, filters were stained with Diff Quick and the number of migrating cells was counted using an imagine analyzer.

Cell adhesion assay

Exponentially growing cells were trypsinized and kept 1 h at 37°C in serum containing medium as for the chemotaxis assay. Then they were resuspended in medium added with 1% FCS and seeded at 30,000 cells/well in 24-well plates coated with gelatin. Tested compounds were added to the wells and the cells were treated for 4 h at 37°C in 5% CO_2. At the end of

the incubation , plates were washed twice with DMEM + 10% FCS. After 48 h of recovery, the cells were counted in a coulter counter. The obtained results are shown in Table III.

TABLE III

EFFECT ON PROLIFERATION OF BAEC CELLS	
	IC_{50} (μM)
FCE 29604	29
C14-ceramide	>100
EFFECT ON A375/M INDUCED MOTILITY OF BAEC CELLS	
	IC_{50} (μM)
FCE 29604	28
C14-ceramide	>100
EFFECT ON ADHESION OF BAEC CELLS	
	IC_{50} (μM)
FCE 29604	< 25
C14-ceramide	>100

Example D

Antiangiogenic activity of benzylcarbinol-derivatives

CAM assay

Chick embryos were removed from their shells on day 3 of development, placed in plastic petri dishes and maintained at 37°C, 3% CO_2. On day 5 the test compound was mixed in methylcellulose disks and placed at the top of growing CAMs. Avascular zones (4 mm in diameter) which represented areas of capillary regression were detected within 48 hrs using a

stereomicroscope.

bFGF-Gelfoam implants

Gelfoam (Upjohn, USA) was cut into strips (approximately 7 by 10 by 10 mm) and loaded with saturating amounts of a 20 µg/ml of bFGF solution in PBS/BSA 0.1%. Control sponges were prepared in the same way and impregnated with PBS/BSA 0.1%. Following induction of anesthesia, a 1-cm-long dorsal midline skin incision was made 3 to 4 cm caudal to the occipital ridge. Sponges were introduced into the subcutaneous pouch and skin was sutured with stample gun. Treatment was administered iv on day 1. After 15 days, mice were sacrificed and sponges were surgically extracted and prepared for histological examination.

The obtained results are shown in Table IV.

TABLE IV

EFFECT ON THE CAM ASSAY			
COMPOUND	**DOSE (nm/pellet)**	**ACTIVITY (% positive CAMs)**	**TOXICITY (% dead embryos)**
FCE 29378	3700	100	0
	1850	67	0
BENZOYLCARBINOL	1850	75	0
EFFECT ON bFGF-GELFOAM			
COMPOUND		**DOSE (mg/Kg)**	**VASCULAR INHIBITION (%)**
FCE 29378		24	85
BENZOYLCARBINOL		200	0

Table IV shows that on the CAM assay FCE 29378 presents an increased activity in comparison with benzoylcarbinol, without increased toxicity. However, in the bFGF-gelfoam assay only the FCE 29378 shows a relevant activity whereas

benzoylcarbinol is completely inactive although tested at higher dose.

The therapeutic regimen in mammals for the different clinical syndromes must be adapted to the type of pathology taking into account, as usual, also the route of administration, the compound, the form in which the compound is administered and the age, weight and conditions of the subject involved.

The dosage level suitable for administration to adult humans of the compounds of the invention, e.g. FCE 28284, FCE 28403 and FCE 29142, may range from about 50 mg to about 1000 mg per dose 1 to 3 times a day, preferably from about 100 mg to about 500 mg per dose 1 to 3 times a day.

Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.

As already said, the present invention includes in its scope also a pharmaceutical composition containing at least a compound of formula (II) in association with a pharmaceutically acceptable carrier or diluent.

The nature of the pharmaceutical composition will, of course, depend upon the desired route of administration.

The compositions may be formulated in the conventional manner with the usual ingredients. For example, the compounds of the invention may be administered in the form of aqueous or oily solutions or suspensions, tablets, pills, capsules, syrups, drops or suppositories.

Thus, for oral administration, the pharmaceutical compositions containing the compounds of this invention are preferably sugar- or film-coated tablets, pills or gelatine capsules which contain the active substance together with diluents, such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance silica, talc, stearic acid, magnesium

or calcium stearate, and/or polyethylene glycols; or they may also contain binders, such as starches, gelatine, methylcellulose, carboxymethylcellulose, gum-arabic, tragacanth, polyvinylpyrrolidone; disaggregating agents, such as starches, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations.

Said pharmaceutical preparations may be manufactured in known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be, e.g., syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspensions or solutions for intramuscular injections may contain together with the active compound a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, Cremophor EL®, glycols, e.g., propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injection or infusion may contain as a carrier, for example, Cremophor EL®, sterile water or, preferably, they may be in the form of sterile aqueous isotonic saline solutions. The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the present invention.

Example 1

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-β-alanyl-2'-taxol [FCE 28284].

To a solution of 2'(β-alanyl)taxol formate, J. Nat. Prod. 51, 298 (1988), (291 mg = 0.3 mmols) in dimethylformamide (20 ml), 4-dimethylaminopyridine (36 mg = 0.3 mmols) and 4-(imidazolyl-carbonylimino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrolecarbonyl-imino))-1,7-naphthalendisulfonic acid disodium salt (246 mg = 0.3 mmols) were added and the whole was stirred at room temperature for 7 hours. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride:methanol 3:1 as eluant, affording 362 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO - d_6) δ: 0.98 (s, 3H, 17), 1.01 (s, 3H, 16), 1.48 (s, 3H, 19), 1.4-1.9 (m, 3H, CH_2-14 + 6β), 1.79 (s, 3H, 18), 2.09, 2.21 (two-s, 6H, CH_3CO-4+CH_3CO-10), 2.30 (m, 1H 6α), 2.60 (m, 2H, $OCO\underline{CH_2}CH_2NH$), 3.30 (m, 2H, $OCOCH_2\underline{CH_2}NH$), 3.[illegible] (d, J=7.3 Hz, 1H, 3), 3.81, 3.84 (two-s, 6H, 2-NCH_3), 3.9-4.[illegible] (m, 3H, CH_2-20+7), 4.63 (s, 1H, OH-1), 4.90 (m, 2H, 5+OH-[illegible]), 5.33 (d, J=8.5 Hz, 1H, 2'), 5.40 (d, J=7.3 Hz, 1H, 2), 5.53 (t, J=8.5 Hz, 1H, 3'), 5.82 (m, 1H, 13), 6.07 (t, J=6.0 Hz, 1H, $CON\underline{H}CH_2CH_2$), 6.28 (s, 1H, 10), 6.77 (d, J=1.7 Hz, 1H, pyrrole), 6.94 (d, J=1.7 Hz, 1H, pyrrole), 7.1-8.0 (m, 21H, 3-Ø+2H pyrrole+2"+3"+6"+5"), 8.22 (s, 1H, $N\underline{H}CONHCH_2CH_2$), 9.17 (d, J=1.8 Hz, 1H, 8"), 9.25 (d, J=8.5 Hz, 1H, NH-4'), 9.86, 10.01

(two-s, 2H, 2-pyrrole CONH).

By analogous procedure the following compounds can be obtained:

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-alanyl-2'-taxol [FCE 28721];

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-alanyl-2'-taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-alanyl-2'(7-epi)taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-alanyl-2'(7-epi)taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-alanyl-2'-taxotere;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-alanyl-2'-taxotere;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-alanyl-3'-etoposide;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-alanyl-3'-etoposide;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-alanyl-3'-doxorubicin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-alanyl-3'-doxorubicin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-alanyl-21-tetrahydro S; and

β-(4-carbonylamino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-alanyl-21-hydrocortisone.

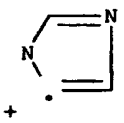
Example 2

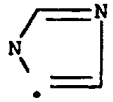
4-(Imidazolyl-carbonyl-imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrolecarbonylimino))-1,7-naphthalendisulfonic acid disodium salt.

The compound 4-(amino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrolecarbonylimino))-1,7-naphthalendisulfonic acid disodium salt, hydrochloride (628 mg = 1 mmol) was dissolved into dimethylformamide (70 ml) and triethylamine (0.14 ml = 1 mmol).

The solution was added dropwise in 3 hours to a solution of N,N'-carbonyldiimidazole (648 mg=4 mmols) in dimethylformamide (40 ml) and the whole was stirred 2 hours at room temperature.

The solvent was evaporated under vacuum to dryness, the residue was treated with acetone (200 ml), stirred for 1 hour and filtered, to obtain the title compound (740 mg).

^{1}H-NMR (200 MHz; DMSO - d_6) δ: 3.86, 3.90 (two-s, 6H, 2-NCH_3), 7.0-7.4 (m, 5H, 4H pyrrol + ), 7.50 (d,J=7.9 Hz, 1H, 3),

7.6-8.1 (m, 4H, 6+5+2+ ), 8.36 (s, 1H, ), 9.20 (s, 1H, 8), 10.05, 10.09, 10.38 (three-s, 3H, 3-CONH).

F.A.B MS : m/z 662, M-Na; 594.

Example 3

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-propionyl-2'taxol [FCE 28403].

To a solution of 2'succinoyl-taxol, J. Med. Chem. 32, 788-792 (1989), (165 mg = 0.173 mmols) in dimethylformamide (15 ml), N,N'dicyclohexylcarbodiimide (71 mg = 0.345 mmols) was added and the mixture stirred for 1 hour.

The compound 4-(amino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrolecarbonyl-imino))-1,7-naphthalendisulfonic acid disodium salt, hydrochloride (155 mg = 0.247 mmols) and 4-dimethylaminopyridine (30 mg = 0.247 mmols) were added and the whole was stirred for 20 hours at room temperature. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride: methanol 3:1 as eluant, affording 180 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO, - d_6) δ: 0.98 (s, 3H, 17), 1.01 (s, 3H, 16), 1.47 (s, 3H, 19), 1.4-1.9 (m, 3H, CH_2-14 + 6β), 1.76 (s, 3H, 18), 2.08, 2.23 (two-s, 6H, CH_3CO-4 + CH_3CO-10), 2.30 (m, 1H, 6α), 2.5-2.8 (m, 4H, $OCOCH_2CH_2CO$), 3.56 (d, J=7.0 Hz, 1H, 3), 3.82, 3.84 (two-s, 6H, 2-NCH_3), 3.9-4.2 (m, 3H, CH_2-20 + 7), 4.61 (s, 1H, OH-1), 4.9 (m, 1H, OH-7 + 5), 5.35 (d, J=9.0

Hz, 1H, 2'), 5.39 (d, J=7.0 Hz, 1H, 2), 5.53 (t, J=9.0 Hz, 1H, 3'), 5.81 (m, 1H, 13), 6.27 (s, 1H, 10), 6.85 (d, J=1.7 Hz, 1H, pyrrole), 7.1-8.0 (m, 22H, 3H-pyrrole + 3-Ø+2"+3"+5" +6"), 9.18 (d, J=1.5 Hz, 8"), 9.23 (d, J=9.0 Hz, 1H, NH-4'), 9.92, 9.96, 10.02 (three-s, 3H, 3-CONH).

By analogous procedure the following compounds can be obtained:

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-propionyl-2'-taxol [FCE 28722];

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-propionyl-2'-taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-propionyl-2'-(7-epi) taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-propionyl-2'-(7-epi) taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-propionyl-2'-taxotere;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-propionyl-2'-taxotere;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-propionyl-20-camptothecin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic

acid trisodium salt)))-propionyl-20-(9-amino) camptothecin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-propionyl-3'-etoposide;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-propionyl-14-(3'-methoxymorpholino)-doxorubicin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-propionyl-1-benzoyl carbinol; and

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))-propionyl-21-hydrocortisone.

Example 4

7-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrole-carbonyl-(N-methyl-4,2-pyrrolecarbonylimino))-1,3,5-naphthalentrisulfonic acid trisodium salt.

The compound 7-(4-amino-N-methyl-2-pyrrolecarbonyl imino-N-methyl-4,2-pyrrolecarbonylimino))-1,3,5-naphthalentrisulfonic acid trisodium salt, hydrochloride (800 mg=1.096 mmol was dissolved into dimethylformamide (80 ml) and triethylamine (0,15 ml=1,096 mmol).

The solution was added dropwise in 3 hours to a solution of N,N'-carbonyldiimidazole (736 mg = 4,384 mmol) in dimethylformamide (60 ml) and the whole was stirred 4 hours at room temperature. The solvent was evaporated under vacuum to dryness, the residue was treated with acetone (250 ml), stirred for 1 hour and filtered, to obtain the title compound (830 mg).

^{1}H-NMR (200 MHz; DMSO d_6) δ: 3.88, 3.89 (two singlets, 6H, 2-NCH_3); 7.0-7.4 (m, 5H, 2-pyrroles + 1H imidazole); 7.79 (s, 1H, imidazole); 8.2-8.4 (m, 3H, 6+2+1H imidazole); 8.9-9.2 (m, 2H, 8+4); 10.04, 10.22, 10.38 (three singlets, 3H, 3-CONH).

By analogous procedure the following compounds can be obtained: 4-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrole carbonyl-imino)-1,7-naphthalendisulfonic acid disodium salt.

^{1}H-NMR (200 MHz, DMSO-d_6) δ: 3.88 (s, 3H, NCH_3); 7.07 (m, 1H, imidazole); 7.23, 7.29 (two doublets, J=1.9 Hz, 2H, pyrrole); 7.48 (d, J=7.7 Hz, 1H, 3); 7.71 (dd, J=7.8 Hz, J=1.8 Hz, 1H, 6); 7.80 (t, J=1.3 Hz, 1H, imidazole); 7.89 (d, J=7.8 Hz, 1H, 5); 7.97 (d, J=7.7 Hz, 1H, 2); 8.36 (m, 1H, imidazole); 9.19 (d, J=1.8 Hz, 1H, 8); 10.06, 10.41 (two singlets, 2H, 2-CONH).

7-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrolecarbonyl-imino)-1,3,5-naphtalentrisulfonic acid trisodium salt.

^{1}H-NMR (200 MHz, DMSO-d_6) δ: 3.91(s, 3H, NCH_3); 7.06 (m, 1H, imidazole); 7.23, 7.26 (two doublets, J=1.9 Hz, 2H, pyrrole); 7.80 (t, J=1.5 Hz, 1H, imidazole); 8.2-8.4 (m, 3H, 6+2+1H imidazole); 9.0, 9.11 (two multiplets, 2H, 8+4); 10.23, 10.37 (two singlets, 2H, 2-CONH).

8-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrolecarbonyl-imino)-1,3,5-naphthalentrisulfonic acid trisodium salt.

Example 5

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic

acid trisodium salt)))-β-alanyl-2'-taxol [FCE 28721].

To a solution of 2'(β-alanyl)taxol formate (97 mg = 0,1 mmol) in dimethylformamide (8 ml), 4-dimethylamino-pyridine (12 mg = 0.1 mmol) and 7-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrolecarbonyl(N-methyl-4,2-pyrrole-carbonylimino))-1,3,5-naphthalentrisulfonic acid trisodium salt (95 mg = 0.12 mmol) were added and the whole was stirred at room temperature for 12 hours. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride: methanol 1:1 as eluant, affording 90 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.99 (s, 3H, 17); 1.01 (s, 3H, 16); 1.49 (s, 3H, 19); 1.80 (s, 3H, 18); 1.5-1.9 (m, 3H, CH_2- 14+6 1H β); 2.09, 2.22 (two singlets, 6H, CH_3CO-4+CH_3CO-10); 2.30 (m, 1H, 6α); 2.60 (m, 2H, $NHCH_2\underline{CH_2}CO$); 3.30 (m, 2H, $NH\underline{CH_2}CH_2CO$); 3.58 (d, J=7.3 Hz, 1H,3); 3.81, 3.88 (two singlets, 6H, 2-NCH_3); 3.98, 4.01 (two doublets, J=8.5 Hz, 2H, CH_2-20); 4.11 (m, 1H, 7); 4.62 (s, 1H, OH-1); 4.89 (m, 2H, 5+OH-7); 5.34 (d, J=8.5 Hz, 1H, 2'); 5.41 (d, J=7.3 Hz, 1H, 2); 5.5 (dd, J=8.5 Hz, J=8.5 Hz, 1H, 3'); 5.83 (m, 1H, 13); 6.06 (m, 1H, $NHCONH\underline{CH_2}$); 6.29 (s, 1H, 10); 6.72, 6.94 (two doublets, J=1.8 Hz, 2H, pyrrole); 7.19, 7.33 (two doublets, J=1.5 Hz, 2H, pyrrole); 7.1, 8.0 (m, 15H, 3-Ph); 8.20 (s, 1H, $NHCONHCH_2$); 8.30 (d, J=1.8 Hz, 1H, 2"); 8.37 (d, J=2.4 Hz, 1H, 6"); 9.00, 9.15 (two multiplets, 2H, 8"+4"); 9.22 (d, J=8.5 Hz, 1H, NH-4'); 9.77, 10.17 (two singlets, 2H, 2-CONH).

Example 6

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-

methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)))propionyl-2'-taxol [FCE 28722].

To a solution of 2'-succinyl-taxol (95 mg = 0.1 mmol) in dimethylformamide (10 ml), N,N'dicycloexylcarbodiimide (41 mg = 0.2 mmol) was added and the mixture stirred for 1 hour. The compound 7-(4-amino,N-methyl-2-pyrrole-carbonyl(4-imino,N-methyl,2-pyrrolecarbonylimino)-1,3,5-naphthalentrisulfonic acid trisodium salt, hydrochloride (80 mg = 0.11 mmol) and 4-dimethylaminopyridine (18 mg = 0.15 mmol) were added and the whole was stirred for 20 hours at room temperature. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride:methanol 1:1 as eluant, affording 120 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.98 (s, 3H, 17); 1.00 (s, 3H, 16); 1.47 (s, 3H, 19); 1.76 (s, 3H, 18); 2.08, 2.23 (two singlets, 6H, CH_3CO-4+CH_3CO-10); 1.4-2.4 (m, 4H, CH_2-14+CH_2-6); 2.5-2.8 (m, 4H, $COCH_2CH_2CO$); 3.56 (d, J=7.0 Hz, 1H, 3); 3.82, 3.87 (two singlets, 6H, 2-NCH_3); 3.9-4.2 (m, 3H, 7+CH_2-20); 4.61 (s, 1H, OH-1); 4.90 (m, 2H, OH-7+5); 5.35 (d, J=8.5 Hz, 1H, 2'); 5.39 (d, J=7.0 Hz, 1H, 2); 5.53 (dd, J=8.5 Hz, J=8.5 Hz, 1H, 3'); 5.81 (m, 1H, 13); 6.27 (s, 1H, 10); 6.81, 7.34 (two doublets, J=1.5Hz, 2H, pyrrole); 7.15, 7.18 (two doublets, J=1.7 Hz, 2H, pyrrole); 7.1-8.0 (m, 15H, 3Ph); 8.29 (d, J=1.7 Hz, 1H, 6"); 8.37 (d, J=2.0 Hz, 1H, 2"); 8.97, 9.13 (two multiplets, 2H, 8"+4"); 9.23 (d, J=8.5 Hz, 1H, 4'); 9.92, 9.93, 10.21 (three singlets, 3H, 3-CONH).

Example 7

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-

naphthalendisulfonic acid disodium salt))β-alanyl-2'-taxol [FCE 28745].

To a solution of 2'(β-alanyl)taxol formate (291 mg = 0.3 mmol) in dimethylformamide (25 ml), 4-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrolecarbonylimino)-1,7-naphthalendisulfonic acid disodium salt (286 mg = 0.5 mmol) was added and the whole was stirred at room temperature for 20 hours. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride: methanol 2:1 as eluant, affording 250 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.99 (s, 3H, 17); 1.01 (s, 3H, 16); 1.48 (s, 3H, 19); 1.4-1.9 (m, 3H, CH_2-14+6β); 1.80 (s, 3H, 18); 2.09, 2.23 (two singlets, 6H, CH_3CO-4+CH_3CO-10); 2.31 (m, 1H, 6α); 2.60 (m, 2H, OCOC$\underline{H_2}CH_2NH$); 3.2-3.5 (m, 2H, $OCOCH_2C\underline{H_2}NH$); 3.58 (d, J=7.3 Hz, 1H, 3); 3.79 (s, 1H, NCH_3); 3.9-4.2 (m, 3H, CH_2-20+7); 4.64 (s, 1H, OH-1); 4.91 (m, 2H, 5+OH-7); 5.34 (d, J=8.5 Hz, 1H, 2'); 5.40 (d, J=7.3 Hz, 1H, 2); 5.54 (dd, J=8.5 Hz, J=8.5 Hz, 1H, 3'); 5.82 (m, 1H, 13); 6.09 (t, J=6.0 Hz, 1H, $OCOCH_2CH_2N\underline{H}$); 6.29 (s, 1H, 10); 6.93-7.02 (two doublets, J=1.9 Hz, 2H, pyrrole); 7.1-8.0 (m, 19H, 3-Ph+3"+6"+5"+ 2"); 8.26 (s, 1H, $N\underline{H}CONHCH_2$); 9.18 (d, J=1.8 Hz, 1H, 8"); 9.25 (d, J=8.5 Hz, 1H, NH-4'); 9.88 (s, 1H, pyrrole-CO$N\underline{H}$).

By analogous procedure the following compounds can be obtained:
N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid trisodium salt))β-alanyl-2'-taxol [FCE 28746].

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.99 (s, 3H, 17); 1.01 (s, 3H, 16); 1.48 (s, 3H, 19); 1.80 (s, 3H, 18); 1.4-1.9 (m, 3H, CH_2-14+6β);

2.09, 2.23 (two singlets, 6H, CH_3CO-4+CH_3CO-10); 2.30 (m, 1H, 6α); 2.60 (m, 2H, $OCOC\underline{H}_2CH_2NH$); 3.2-3.5 (m, 2H, $OCOCH_2C\underline{H}_2NH$); 3.58 (d, J=7.0 Hz, 1H, 3); 3.83 (s, 3H, NCH_3); 3.9-4.2 (m, 3H, CH_2-20+7); 4.64 (s, 1H, OH-1); 4.90 (m, 2H, 5+OH-7); 5.34 (d, J=8.5 Hz, 1H, 2'); 5.40 (d, J=7.0 Hz, 1H, 2); 5.54 (dd, J=8.5 Hz, J=8.5 Hz, 1H, 3'); 5.82 (m, 1H, 13); 6.12 (m, 1H, $OCOCH_2CH_2N\underline{H}$); 6.29 (s, 1H, 10); 6.91, 7.01 (two doublets, J=1.8 Hz, 2H, pyrrole); 7.1-8.0 (m, 15H, 3-Ph); 8.22 (s, 1H, $N\underline{H}CONHCH_2$); 8.26 (d, J=1.8 Hz, 1H, 2"); 8.34 (d, J=2.3 Hz, 1H, 6"); 8.94, 9.10 (two multiplets, 2H, 8"+4"); 9.27 (d, J=8.5 Hz, 1H, NH-4'); 10.02 (s, 1H, pyrrole-CO$N\underline{H}$).

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt))-β-alanyl-2'-taxol [FCE 28842].

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.00 (s, 3H, 17); 1.02 (s, 3H, 16); 1.49 (s, 3H, 19); 1.81 (s, 3H, 18); 1.4-1.9 (m, 3H, CH_2-14+6β); 2.10, 2.24 (two singlets, 6H, CH_3CO-4+CH_3CO-10); 2.2-2.4 (m, 1H, 6α); 2.60 (m, 2H, $OCOC\underline{H}_2CH_2NH$); 3.1-3.3 (m, 2H, $OCOCH_2C\underline{H}_2NH$); 3.59 (d, J=7.2 Hz, 1H, 3); 3.82 (s, 3H, NCH_3); 3.9-4.2 (m, 3H, CH_2-20+7); 4.65 (s, 1H, OH-1); 4.93 (m, 2H, 5+OH-7); 5.34 (d, J=8.5 Hz, 1H, 2'); 5.41 (d, J=7.2 Hz, 1H, 2); 5.54 (dd, J=8.5 Hz, J=8.5 Hz, 1H, 3'); 5.83 (m, 1H, 13); 6.02 (t, J=6.0 Hz, 1H, $OCOCH_2CH_2N\underline{H}$); 6.30 (s, 1H, 10); 6.95, 7.03 (two doublets, J=1.7 Hz, 2H, pyrrole); 7.1-8.1 (m, 17H, 3-Ph+7"+ 6"); 8.34 (s, 1H, $N\underline{H}CONHCH_2$); 8.61 (d, J=2 Hz, 1H, 2"); 9.27 (d, J=8.5 Hz, 1H, NH-4'); 9.37 (d, J=2.0 Hz, 1H, 4"); 12.20 (s, 1H, pyrrole-CO$N\underline{H}$).

Example 8

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt))phenylalanyl-leucyl-glycyl-2'-taxol [FCE 29142].

To a solution of 2'(phenylalanyl-leucyl-glycyl)taxol (351 mg = 0.3 mmol) (WO 94/00156) in dimethylformamide (20 ml), 4-dimethylaminopyridine (36 mg = 0.3 mmol) and 8-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrole carbonylimino)-1,3,5-naphthalenetrisulfonic acid trisodium salt (333 mg = 0.5 mmol) were added and the whole was stirred at room temperature for 20 hours. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride: methanol 2:1 as eluant, affording 331 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.81 (d, J=6.5 Hz, 3H, δ-Leu); 0.84 (d, J=6.5 Hz, 3H, δ'-Leu); 0.99 (s, 3H, 17); 1.01 (s, 3H, 16); 1.48 (s, 3H, 19); 1.79 (s, 3H, 18); 1.4-1.9 (m, 6H, CH_2-14+6β+γLeu+β,β'Leu); 2.09, 2.21 (two singlets, 6H, CH_3CO-4+CH_3CO-10); 2.32 (m, 1H, 6α); 2.81 (dd, J=7.9 Hz, J=13.7 Hz, 1H, βPhe); 2.99 (dd, J=4.1 Hz, J=13.7 Hz, 1H, β'Phe); 3.57 (d, J=8.2 Hz, 1H, 3); 3.78 (s, 3H, NCH_3); 3.8-4.2 (m, 5H, α, α'Gly+CH_2-20+7); 4.38 (m, 1H, αLeu); 4.48 (m, 1H, αPhe); 4.61 (s, 1H, OH-1); 4.90 (m, 2H, OH-7+5); 5.40 (m, 2H, 2'+2); 5.51 (dd, J=8.5 Hz, J=8.5 Hz, 1H, 3'); 5.84 (m, 1H, 13); 6.03 (d, J=7.9 Hz, 1H, NH-Phe); 6.29 (s, 1H, 10); 6.91-7.00 (two doublets, J=1.9 Hz, 2H, 3"'+5"'); 7.1-8.1 (m, 22H, 4 Ph+6"+7"); 8.15 (d, J=8.5 Hz, 1H, NH-Leu); 8.39 (t, J=6.0 Hz, 1H, NH-Gly); 8.50 (s, 1H, NH-4"'); 8.60 (d, J=2.0 Hz, 1H, 7"); 9.26 (d, J=8.2 Hz, 1H, NH-4'); 9.36 (d, J=2.0 Hz, 1H, 4"); 12.18 (s, 1H,

NH-8").

Example 9

3'-N-Succinyldaunorubicin.

Daunorubicin (100 mg, 0.177 mmol) and succinic anhydride (21.2 mg, 0.212 mmol) were dissolved into dry methylene chloride (20 ml). Triethylamine (123 µl, 0.885 mmol) was then added and the whole was stirred at room temperature, under N_2, for 2.5 hours.The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride:methanol 7:3 as eluant, affording the title compound (120 mg).

Example 10

3-(4-Carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl-2-pyrrolecarbonyl-(7-imino-1,3-naphthalendisulfonic acid disodium salt)))propionyl-3'-N-daunorubicin [FCE 28854].

The compound 3'-N-succinyldaunorubicin (87 mg, 0.139 mmol) and 1,1'-carbonyldiimidazole (22.5 mg, 0.139 mmol) were dissolved into dimethylformamide (10 ml) and the whole was stirred at room temperature, under N_2, for 8 hours. The compound 7-(amino-N-methyl-4,2-pyrrolecarbonylimino(N-methyl-4,2-pyrrolecarbonyl-imino))-1,3-naphthalendisulfonic acid disodium salt, hydrochloride (109 mg, 0.139 mmol) and 4-dimethylaminopyridine (18.3 mg, 0.15 mmol) were then added and the whole was stirred overnight. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a LiChroprep RP-8 column with water : acetonitrile 4 : 1 as eluant, affording the title compound (57 mg).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.12 (d, J=6.6 Hz, 3H, CH_3-6'); 1.42 (dd, J=4.5 Hz, J=12.1 Hz, 1H, 2'eq); 1.84 (m, 1H, 2' ax); 2.1-2.3 (m, 2H, CH_2-8); 2.25 (s, 1H, $COCH_3$); 2.3-2.5 (m, 4H, $COCH_2CH_2CO$); 2.92, 2.98 (two doublets, J=18.2 Hz, 2H, CH_2-10); 3.40 (m, 1H, 4'); 3.86, 3.80 (two singlets, 6H, 2-NCH_3); 3.97 (s, 3H, OCH_3); 3.95 (m, 1H, 3'); 4.17 (q, J=6.6 Hz, 1H, 5'); 4.73 (d, J=5.9 Hz, 1H, OH-4'); 4.93 (m, 1H, 7); 5.22 (d, J=3.1 Hz, 1H, 1'); 5.54 (s, 1H, OH-9); 6.81, 7.12, 7.14, 7.31 (four doublets, J=1.7 Hz, 4H, pyrroles); 7.60 (d, J=8.0 Hz, 1H, NH-3'); 7.64 (m, 1H, 3); 7.90 (m, 4H, 1+2+5"+6"); 8.00 (d, J=1.8 Hz, 1H, 4"); 8.22 (d, J=1.8 Hz, 1H, 2"); 8.90 (d, J=1.8 Hz, 1H, 8"); 9.81, 9.90, 10.21 (three singlets, 3H, 3-CONH); 13.29, 14.04 (two singlets, 2H, OH-6 + OH-11).

F.A.B MS : m/z 1178 , M^--Na

Example 11

20-O-(Carbobenzyloxy-β-alanyl)camptothecin.

Carbobenzyloxy-β-alanine (3.2 g, 14.34 mmol) and 4-dimethylaminopyridine (3.5 g, 28.68 mmol) were dissolved into dry chloroform (30 ml) and, under stirring, under nitrogen, oxalyl chloride (1.24 ml, 14.34 mmol) was added dropwise. After 45 min the crude reaction mixture was added, avoiding contact with air, to a suspension of camptothecin (2.5 g, 7.17 mmol) and 4-dimethylamino pyridine (875 mg, 7.17 mmol) in 1,2-dichloroethane (100 ml) and the whole was stirred, under nitrogen, for 2 hours. The reaction solution was diluted with methylene chloride (100 ml) and washed with water (200 ml). The organic layer was separated, dried and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol (150 ml) affording the title compound (3.47 g).

^{1}H-NMR (200 MHz ; DMSO d_6) δ: 0.95 (t, 3H, $\underline{CH_3}CH_2$); 2.15 (q, 2H, $CH_3\underline{CH_2}$); 2.75 (m, 2H, $NHCH_2\underline{CH_2}COO$); 3.3 (m, 2H, $NH\underline{CH_2}CH_2COO$); 5.0 (s, 2H, $Ph\underline{CH_2}$); 5.25 (s, 2H, CH_2-5); 5.5 (s, 2H, CH_2-17); 7.1 (s, 1H, 14); 7.2-7.4 (m, 6H, Ph+$N\underline{H}$); 7.7 (m, 1H, 10); 7.85 (m, 1H, 11); 8.15 (m, 2H, 12+9); 8.65 (s, 1H, 7).

Example 12

20-O-(β-alanyl)camptothecin, formic acid salt

To a solution of 20-O-(Carbobenzyloxy-β-alanyl)camptothecin (3.0 g, 5.42 mmol) in methanol (170 ml) and formic acid (100 ml), 5% Pd/C (1.0 g) was added and the whole was stirred at 40°C for 4 hours. The reaction mixture was filtered and the solvent was evaporated in vacuum to dryness, affording the title compound (2.5 g).

^{1}H-NMR (200 MHz ; DMSO d_6) δ: 0.95 (t, 3H, $\underline{CH_3}CH_2$); 2.15 (q, 2H, $CH_3\underline{CH_2}$); 2.7-3.1 (m, 4H, $NH\underline{CH_2}\underline{CH_2}COO$); 5.3 (s, 2H, CH_2-5); 5.5 (s, 2H, CH_2-17); 7.15 (s, 1H, 14); 7.7 (m, 1H, 10); 7.85 (m, 1H, 11); 8.15 (m, 2H, 12+9); 8.3 (bs, 1H, $\underline{H}CO_2H$); 8.7 (s, 1H, 7).

Example 13

N-(4-Carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino,1,7-naphthalendisulfonic acid disodium salt)))-β-alanyl-20-O-camptothecin [FCE 28855].

The compound 20-O-(β-alanyl)camptothecin, formic acid salt (200 mg, 0.43 mmol) and 4-(imidazolyl-carbonyl-imino-N-methyl-4,2-pyrrolecarbonylimino(N-methyl-4,2-pyrrolecarbonylimino))-1,7-naphthalendisulfonic acid disodium salt (354 mg, 0.516

mmol) were dissolved into dimethylformamide (10 ml) and the whole was stirred at room temperature under N_2 for 8 hours. The solvent was removed under reduced pressure and the residue was treated with methylene chloride (30 ml), stirred for 30 min and filtered to obtain a crude product which was chromatographed on a LiChroprep RP-8 column affording the title product (165 mg). The eluant system was a gradient from A to B where A was water and B was water:acetonitrile 85:15.

^{1}H-NMR (400 MHz ; DMSO d_6) δ : 0.9 (t, J=7.4 Hz, 3H, $\underline{CH_3}CH_2$); 2.16 (q, J=7.4 Hz, 2H, $CH_3\underline{CH_2}$); 2.73 (m, 2H, $NHCH_2\underline{CH_2}COO$); 3.30 (m, 2H, $NH\underline{CH_2}CH_2COO$); 3.76, 3.84 (two singlets, 6H, 2-NCH_3); 5.30 (s, 2H, CH_2-5); 5.49 (s, 2H, CH_2-17); 6.03 (t, J=6.0 Hz, 1H, $N\underline{H}CH_2CH_2COO$); 6.68, 6.86, 7.18, 7.35 (four doublets, J=1.7 Hz, 4H, pyrroles); 7.10 (s, 1H, 14); 7.49 (d, J=7.8 Hz, 1H, 3'); 7.68 (m, 2H, 10+6'); 7.81 (m, 1H, 11), 7.89 (d, J=8.6 Hz, 1H, 5'); 7.96 (d, J=7.8 Hz, 1H, 2'); 8.09 (m, 2H, 12+9); 9.19 (s, 1H, $CH_2NHCON\underline{H}$); 8.68 (s, 1H, 7); 9.18 (d, J=1.5 Hz, 1H, 8'); 8.79, 10.00 (two singlets, 2H, 2-CONH).

F.A.B MS : m/z 991, M^--2Na+H ; 1013, M^--Na

By proceeding analogously, the following compound can be obtained:

N-(4-Carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino,1,7-naphthalendisulfonic acid disodium salt)))-phenylalanyl-leucyl-glycyl-10-camptothecin.

Example 14

O-(N-Trityl-phenylalanyl-leucyl-glycyl)benzoylcarbinol.

To a solution of benzoylcarbinol (408 mg, 3 mmol) in 20 ml of

pyridine, were added 4-dimethylamino-pyridine (244 mg, 2 mmol) and N-trityl-phenylalanyl-leucyl-glycine-4-nitrophenylester (1398 mg, 2 mmol) and the whole was stirred at reflux for 6 hours. The reaction mixture was diluted with ethylacetate, washed with diluted hydrochloric acid (0.5 N), water and dried on anhydrous sodium sulphate.

The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with ethylacetate:hexane 1:1 as eluant, affording 930 mg of the title compound.

Example 15

O-(phenylalanyl-leucyl-glycyl)benzoylcarbinol.

The compound O-(N-trityl-phenylalanyl-leucyl-glycyl) benzoylcarbinol (930 mg) was dissolved into a mixture of glacial acetic acid (110 ml) and water (25 ml) and the whole was stirred for 1,5 hours at room temperature. The solvents were evaporated under vacuum to dryness, the residue was dissolved in ethylacetate, diluted with toluol and evaporated, affording 606 mg of the crude compound.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.89, 0.91 (two doublets, J=6.1Hz, 6H, $\delta+\delta'$-Leu); 1.4-1.8 (m, 3H, $\beta+\beta'+\gamma$-Leu); 2.72 (dd, J=9.0, 13.6Hz, 1H, β-Phe); 3.20 (dd, J=4.0, 13.6Hz, 1H, β'-Phe); 3.68 (dd, J=4.0, 9.0Hz, 1H, α-Phe); 4.0-4.4 (m, 2H, $\alpha+\alpha'$-Gly); 4.52 (m, 1H, α-Leu); 5.37 (s, 2H, $COOCH_2$); 7.0-8.0 (m, 12H, 2-Ph + NH - Leu + NH-Gly).

Example 16

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-

naphthalentrisulfonic acid trisodium salt))phenylalanyl-leucyl-glycyl-O-benzoylcarbinol [FCE 29378].

To a solution of O-(phenylalanyl-leucyl-glycyl) benzoylcarbinol (600 mg) in dimethylformamide (100 ml), 4-dimethylaminopyridine (160 mg) and 8-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrolecarbonylimino)-1,3,5-naphthalene-trisulfonic acid trisodium salt (1068 mg) were added and the whole was stirred at room temperature for 20 hours. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride:methanol 2:1 as eluant, affording 702 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 0.83,0.87(two d,J=6.6Hz,6H,$\delta+\delta'$-Leu); 1.4-1.7(m, 3H, $\beta+\beta'+\gamma$-Leu); 2.80 (dd,J=7.7,13.5Hz,1H,β-Phe); 3.1 (dd,J=4.8,13.5Hz,1H,β'-Phe); 3.80 (s,3H,NCH_3); 3.9-4.1 (m,2H,$\alpha+\alpha'$-Gly); 4.38 (m,1H,α-Leu); 4.47 (m,1H,α-Phe); 5.50,5.53 (two d, J=17.3Hz, 2H, $COOCH_2CO$); 6.03 (d, J=8.1Hz, 1H, NH-Phe); 6.91, 7.01 (two d, J=1.6Hz, 2H, 3'+5'); 7.1-8.0 (m, 10H, 2-Ph); 8.00, 8.05 (two d, J=8.3Hz, 2H, 6+7); 8.18 (d, J=8.4Hz, 1H, NH-Leu); 8.37 (t, J=5.9Hz, 1H, NH-Gly); 8.49 (s, 1H, NH-4'); 8.60 (d, J=2.0Hz, 1H, 2); 9.36 (d, J=2.0Hz, 1H, 4); 12.18 (s, 1H, NH-1).

By analogous procedure the following compound can be obtained:

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt))phenylalanyl-leucyl-glycyl-β-alanyl-O-benzoylcarbinol.

Example 17

21-(N-Trityl-phenylalanyl-leucyl-glycyl)hydrocortisone.

To a solution of hydrocortisone (362 mg, 1 mmol) in 15 ml of pyridine, were added 4-dimethylamino-pyridine (122 mg, 1 mmol) and N-trityl-phenylalanyl-leucyl-glycine-4-nitrophenylester (769 mg, 1.1 mmol) and the whole was stirred at 100°C for 3 hours. The reaction mixture was diluted with ethylacetate, washed with diluted hydrochloric acid (0.5 N), water and dried on anhydrous sodium sulphate.
The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with ethylacetate:hexane 3:1 as eluant, affording 750 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.75 (s, 3H, 18); 0.83, 0.86 (two d, J=6.4Hz, 6H, δ+δ'-Leu); 1.35 (s, 3H, 19); 2.7[illegible] d, J=8.8Hz, NH-Phe); 3.40 (m, 1H, α-Phe); 3.7-4.0 (m, 3H, α-Leu + α,α'-Gly); 4.24 (m, 1H, 11); 4.31 (d, J=3.8Hz, 1H, OH-[illegible]; 4.74, 5.13 (two d, J=17.6Hz, 2H, CH_2-21); 5.39 (s, 1H, [illegible]-17); 5.54 (s, 1H, 4); 7.0-7.4 (m, 20H, 4-Ph); 7.[illegible] J=7.6Hz, 1H, NH-Leu); 8.18 (t, J=6.0Hz, 1H, NH-Gly).

Example 18

21-(phenylalanyl-leucyl-glycyl)hydrocortisone.

A mixture of 21-(N-trityl-phenylalanyl-leucyl-g[illegible] hydrocortisone (750 mg) in glacial acetic acid (115 ml [illegible] water (25 ml) was stirred for 3 hours at room temperature. The solvents were evaporated under vacuum to dryness, the residue was dissolved in methanol, diluted with toluol and

evaporated. The residue was chromatographed on a silica gel column with ethylacetate:methanol 5:1 as eluant, affording 400 mg of the title compound.

F.A.B. MS: m/z 678, M-H.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.74 (s, 3H, 18); 0.83, 0.85 (two d, J=6.2Hz, 6H, δ+δ'-Leu); 1.34 (s, 3H, 19); 2.61 (dd, J=8.5, 13.5Hz, 1H, β-Phe); 2.93 (dd, J=4.4, 13.5Hz, 1H, β'-Phe); 3.42 (dd, J=4.4, 8.5Hz, 1H, α-Phe); 3.87 (dd, J=6.0, 17.6Hz, 1H, α-Gly); 3.96 (dd, J=6.0, 17.6Hz, 1H, α'-Gly); 4.25 (m, 1H, 11); 4.36 (m, 2H, OH-11 + α-Leu); 4.76, 5.13 (two d, J=17.6Hz, 2H, CH_2-21); 5.42 (s, 1H, OH - 17); 5.54 (s, 1H, 4); 7.1-7.3 (m, 5H, Ph); 7.95 (d, J=7.8Hz, 1H, NH-Leu); 8.38 (t, J=6.0Hz, 1H, NH-Gly).

Example 19

21-(N-(4-carbonylimino, N-methyl, 2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt))phenylalanyl-leucyl-glycyl)hydrocortisone [FCE 29603].

To a solution of 21-(phenylalanyl-leucyl-glycyl) hydrocortisone (400 mg, 0.59 mmol) in dimethylformamide (30 ml), 4-dimethylaminopyridine (72 mg, 0.59 mmol) and 8-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrolecarbonylimino)-1,3,5-naphthalenetrisulfonic acid trisodium salt (609 mg, 0.915 mmol) were added and the whole was stirred at room temperature for 6 hours. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride:methanol 2:1 as eluant, affording 390 mg of the title compound.

F.A.B. MS: m/z 1010, M-H (as free acid).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.76 (s, 3H, 18); 0.83, 0.87 (two d, J=6.6Hz, 6H, δ+δ'-Leu); 1.34 (s, 3H, 19); 2.80 (dd, J=8.0, 13.9Hz, 1H, β-Phe); 3.00 (dd, J=4.4, 13.9Hz, 1H, β'-Phe); 3.80 (s, 3H, NCH_3); 3.87 (dd, J=17.6, 6.1Hz, 1H, α-Gly); 4.00 (dd, J=17.6, 6.1Hz, 1H, α'-Gly); 4.24 (m, 1H, 11); 4.35 (m, 2H, OH11 + α-Leu); 4.46 (m, 1H, α-Phe); 4.77, 5.14 (two d, J=17.6Hz, 2H, CH_2-21); 5.43 (s, 1H, OH - 17); 5.54 (s, 1H, 4); 6.02 (d, J=7.7Hz, 1H, NH-Phe); 6.90, 7.00 (two d, J=1.8Hz, 2H, 3'+5'); 7.1-7.3 (m, 5H, Ar-Phe); 8.00, 8.04 (two d, J=8.4Hz, 2H, 6"+7"); 8.16 (d, J=8.4Hz, 1H, NH-Leu); 8.31 (t, J=6.1Hz, 1H, NH-Gly); 8.48 (s, 1H, CONH-4'); 9.61 (d, J=1.8Hz, 1H, 2"); 9.38 (d, J=1.8Hz, 1H, 4"); 12.17 (s, 1H, CONH-8").

Example 20

Tallimustine amidoxime.

A solution of 500 mg of tallimustine (prepared as reported in J.Med.Chem. 32, 774-778, 1989) in 20 ml of DMF was heated at 60°C and treated with 0.68 ml of hydroxylamine 1M in DMF, obtained from hydroxylamine hydrochloride (70 mg), 0.139 ml of triethylamine and 1 ml of DMF with 10% water.
After 30' additional 1 equivalent of hydroxylamine 1M in DMF was added. The solution was evaporated to dryness and the residue was purified by flash chromatography (methylene chloride:methanol 85:15) to give 400 mg of the title compound as a white solid.

F.A.B. MS: m/z 713, M+H; 244.

^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.20 (m, 2H); 3.32 (m, 2H); 3.79

(s, 3H); 3.83 (s, 3H); 3.85 (s, 3H); 3.90-3.70 (m, 8H); 5.40 (bs, 2H); 6.82 (m, 2H); 6.83 (d, J=1.7 Hz, 1H); 7.4 (d, J=1.7 Hz, 1H); 7.6 (d, J=1.7 Hz, 1H); 7.17 (d, 1.7 Hz, 1H); 7.23 (d, 1.7 Hz, 1H); 7.28 (d, J=1.7 Hz, 1H); 7.83 (m, 2H); 7.87 (t, J=5.7 Hz, 1H); 8.82 (s, 1H); 9.86 (s, 1H); 9.92 (s, 1H); 9.98 (s, 1H).

Example 21

O-(N-Trityl-phenylalanyl-leucyl-glycyl)tallimustine amidoxime.

To a solution of tallimustine amidoxine (250 mg, 0.35 mmol) in dimethylformamide (9 ml), 4-dimethylamino-pyridine (48 mg, 0.35 mmol) and N-trityl-phenylalanyl-leucyl-glycine-4-nitrophenylester (315 mg, 0.45 mmol) were added and the whole was stirred at room temperature for 4 hours.
The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylenechloride:methanol 28:2 as eluant, affording 357 mg of the title compound.

Example 22

O-(phenylalanyl-leucyl-glycyl)tallimustine amidoxime.

A mixture of O-(N-trityl-phenylalanyl-leucyl-glycyl) tallimustine amidoxime (314 mg) in glacial acetic acid (28 ml) and water (6.5 ml) was stirred for 1 hour at room temperature. The solvents were evaporated under vacuum to dryness, the residue was dissolved in methanol, diluted with toluol and evaporated, affording 254 mg of the crude compound.

F.A.B. MS: m/z 1031, M+H; 697, M -(O-GlyLeu-Phe)+2H; 336; 261; 244.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.83,0.86 (two doublets, J=6.4 Hz, 6H, δ+δ'-Leu); 1.3-1.5 (m, 3H, β+β'+γ-Leu); 2.31 (t, J=7.5 Hz, 2H, CONHCH$_2$CH$_2$); 2.63 (dd, J=13.3, 8.2 Hz, 1H, β-Phe); 2.94 (dd, J=13.3, 4.4Hz, 1H, β'-Phe); 3.2-3.4 (m, 3H, CONHCH$_2$CH$_2$+α-Phe); 3.6-4.0 (m, 19H, 3-NCH$_3$+α,α'-Gly+ N(CH$_2$CH$_2$Cl)$_2$); 4.36 (m, 1H, α-Leu); 6.45 (bs, 2H, NH$_2$); 6.7-7.4 (m, 13H, 6H pyrroles+Ar-Phe+2H Ph); 7.85 (m, 2H, Ph); 8.03 (m, 2H, NH-Leu + CONHCH$_2$CH$_2$); 8.33 (t, J=5.9 Hz, 1H, NH-Gly); 9.91,9.95,10.02 (three singlets, 3H, 3-CONH).

Example 23

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt))phenylalanyl-leucyl-glycyl)-O-tallimustine amidoxime.

To a solution of O-(phenylalanyl-leucyl-glycyl)tallimustine amidoxime (254 mg, 0.246 mmol) in dimethylformamide (30ml), 4-dimethylaminopyridine (30 mg, 0.246 mmol) and 8-(4-(imidazolyl-carbonyl-imino)-N-methyl-2-pyrrolecarbonylimino)-1,3,5-naphthalenetrisulfonic acid trisodium salt (172 mg, 0.258 mmol) were added and the whole was stirred at 50°C for 4 hours. The solvent was evaporated under vacuum to dryness and the residue was chromatographed on a silica gel column with methylene chloride:methanol 7:3 as eluant, affording 240 mg of the title compound.

F.A.B. MS: m/z 1561, M-H(as free acid).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.83,0.87 (two doublets, J=6.6 Hz, 6H, δ+δ'-Leu); 1.4-1.7 (m, 3H, β+β'+γ-Leu); 2.31 (t,

J=7.5 Hz, 2H, $CONHCH_2\underline{CH_2}$); 2.81 (dd, J=13.7, 8.0 Hz, 1H, β-Phe); 3.00 (dd, J=13.7, 4.4Hz, 1H, β'-Phe); 3.3-3.5 (m, 2H, $CONH\underline{CH_2}CH_2$); 3.7-4.1 (m, 22H, $4\text{-}NCH_3$+α,α'-Gly+ $N(CH_2CH_2Cl)_2$); 4.35 (m, 1H, α-Leu); 4.45 (m, 1H, +α-Phe); 6.2 (d, J=7.7 Hz, 1H, NH-Phe); 6.45 (bs, 2H, NH_2); 6.7-7.3 (m, 15H, 8H pyrroles+Ar-Phe+2H Ph); 7.84 (m, 2H, Ph);7.9-8.1(m, 3H, $CONHCH_2CH_2$+6+7); 8.18 (d, J=8.4 Hz, 1H, NH-Leu); 8.25 (t, J=5.9 Hz, 1H, NH-Gly); 8.47 (s, 1H, NH-4'); 8.61 (d, J=2.6 Hz, 1H, 2); 9.37 (d, J=2.6 Hz, 1H, 4); 9.88,9.92,10.0,12.2 (four singlets, 4H, 4-CONH).

Example 24

7-(imidazolyl-carbonylimino-N-methyl-4,2-pyrrolecarbonyl-imino)-1,3-naphthalendisulfonic acid dipotassium salt.

To a stirred solution of N,N'-carbonyldiimidazole (1.48 g, 9.14 mmol) in dimethylformamide (5 ml), under N_2, a solution of 7-(4-amino-N-methyl-2-pyrrolecarbonylimino)-1,3-naphthalendisulfonic acid dipotassium salt (458 mg, 0.914 mmol) in dimethylformamide (5 ml) was added dropwise, at room temperature, in 1 hour.

After 3.5 hours the reaction mixture was concentrated under reduced pressure to 3 ml and acetone (100 ml) was then added. The solid precipitated was filtered and washed with acetone affording the title compound (476 mg, pink powder).

^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.95 (s, 3H); 7.1 (m, 1H); 7.25 (d, 1H); 7.3 (d, 1H); 7.8 (t, 1H); 7.9 (m, 2H); 8.0 (m, 1H); 8.25 (d, 1H); 8.4 (m, 1H); 8.95 (bs, 1H); 10.3 (bs, 1H); 10.4 (bs, 1H).

Example 25

N-tetradecanoylimidazole.

To a solution of myristic acid (1.0 g, 4.38 mmol) in ethyl acetate (10 ml) N,N'-carbonyldiimidazole (697 mg, 4.3 mmol) was added in small portions. The whole was stirred at room temperature for 2 hours after which evolution of CO_2 ceased and the precipitation of a white crystalline solid was observed.

The solid was filtered, washed with ethyl acetate (few ml) and dried affording the title compound (566 mg).

^{1}H-NMR (200 MHz, DMSO-d_6): δ 0.85 (t, 3H); 1.1-1.4 (m, 20 H); 1.55-1.75 (m, 2H); 3.0 (t, 2H); 7.05 (m, 1H); 7.7 (t, 1H); 8.4 (m, 1H).

Example 26

(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene (C_{14}-ceramide).

To a solution of (2S,3R,4E)-1,3-dihydroxy-2-amino-4-octadecene (D-sphingosine, Fluka, 100 mg, 0.334 mmol) in dichloromethane (15 ml), 93 mg of N-tetradecanoylimidazole (0.334 mmol) were added in one portion and the whole was stirred at room temperature for 90 hours.

The solvent was then removed under reduced pressure and the residue purified by flash chromatography on a silica gel column with CH_2Cl_2:EtOH 95:5 as eluant, affording the title compound (148 mg, white solid).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.75-0.95 (m, 6H); 1.1-1.5 (m,

40H); 1.5-1.7 (m, 4H); 1.95-2.1 (m, 2H); 2.2 (t, 2H); 2.7-2.8 (m, 2H); 3.6-3.8 (m, 1H); 3.85-4.0 (m, 2H); 4.25-4.35 (m, 1H); 5.45-5.6 (m, 1H); 5.7-5.85 (m, 1H); 6.2 (d, 1H).

Example 27

1-O-(N-tritylphenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene.

To a stirred solution of (2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene (142 mg, 0.28 mmol) and 4-dimethylaminopyridine (68 mg, 0.56 mmol) in dry 1,2-dichloroethane (50 ml), N-tritylphenylalanyl-leucyl-glycine p-nitrophenylester (195 mg, 0.28 mmol), dissolved in 1,2-dichloroethane (10 ml), was added dropwise, under N_2, at room temperature and the whole was stirred for 4 days.
The solvent was removed under reduced pressure and the residue purified by flash chromatography on a silica gel column with petroleum ether:ethyl acetate 1:1 as eluant, affording the title compound (106 mg, colourless oil).

Example 28

1-O-(phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene.

To a mixture of acetic acid (10 ml) and water (2 ml) 1-O-(N-tritylphenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene (106 mg, 0.1 mmol) was added and the whole was stirred at room temperature for 3 hours.
The solvent was removed under reduced pressure and the residue purified by flash chromatography on a silica gel column with EtOAc:EtOH 85:15 as eluant, affording the title compound (65 mg, white solid).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.8-1.0 (m, 12 H); 1.1-2.1 (three groups of multiplets , 52 H); 2.25 (t, 2H); 2.75 (dd, 1H); 3.2 (dd, 1H); 3.7 (dd, 1H); 3.8-4.25 (m, 5H); 4.3-4.5 (m, 2H); 5.4-5.5 (m, 1H); 5.65-5.85 (m, 1H); 6.5 (d, 1H); 6.95 (t, 1H); 7.15-7.4 (m, 5H); 7.75 (d, 1H).

Example 29

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid dipotassium salt))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene [FCE 29604A].

The compound 1-O-(phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene (65 mg, 0.078 mmol) was dissolved into dry dimethylformamide (10 ml) and 7-(imidazolyl-carbonylimino-N-methyl-4,2-pyrrolecarbonyl-imino)-1,3-naphthalendisulfonic acid dipotassium salt (59.5 mg, 0.1 mmol) was added in one portion. The whole was stirred for 2 hours at room temperature, then the solvent was removed under reduced pressure and the residue purified by flash chromatography on a silica gel column with CH_2Cl_2:MeOH 3:1 then 2:1 as eluant, affording the title compound (56 mg, white solid).

F.A.B. MS: m/z 1276, M-2K+H.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.8-0.9 (m, 12H, δ,δ'-Leu+2-$\underline{CH_3}(CH_2)_{11}CH_2$); 1.1-1-4 (m, 44H, 2-$CH_3(\underline{CH_2})_{11}CH_2$); 1.4-1.7 (m, 3H, β,γ,γ'-Leu); 1.92 (m, 2H, CH_2-6); 2.03 (t, J=7.5 Hz, 2H, $\underline{CH_2}$CONH-2); 2.82 (dd, J=13.8, 7.9Hz, 1H, β-Phe); 3.01 (dd, J=13.8, 4.7Hz, 1H, β'-Phe); 3.7-3.9 (m, 4H, α,α'-Gly+2+3); 4.0-4.3 (m, 2H, CH_2-1); 4.36 (m, 1H, α-Leu);

4.50 (m, 1H, α-Phe); 5.00 (d, J=5.3 Hz, 1H, OH-3); 5.34 (dd, J=6.4, 15.5Hz, 1H, 4); 5.56 (dt,J=15.5, 6.4Hz, 1H, 5); 6.10 (d, J=7.8Hz, 1H, NH-Phe); 6.85-6.9 (two doublets, J=1.8Hz, 2H, 3A+5A); 7.1-7.3 (m, 5H, Ar-Phe); 7.54 (d, J=8.8Hz, 1H, NH-2); 7.84 (d, J=9.1Hz, 1H, 5B); 7.89 (dd, J=9.1, 2.0Hz, 1H, 6B); 8.00 (d, J=1.8 Hz, 1H, 4B); 8.1-8.3 (m, 3H, 2B+NHGly+NHLeu); 8.31 (s, 1H, NH_A); 8.83 (d, J=2.0Hz, 1H, 8B); 10.02 (s, 1H, NH_B).

By analogous procedure the following compounds can be obtained:

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid disodium salt))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-acetylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid disodium salt))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-exanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid disodium salt))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid disodium salt))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid disodium salt))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-acetylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid disodium salt))β-alanyl)-

(2S,3R,4E)-1,3-dihydroxy-2-exanoylamido-4-octadecene;
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid disodium salt))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene;
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)) phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene; and
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(8-imino-1,3,5-naphthalentrisulfonic acid trisodium salt)) phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene.

Example 30

7-epi-taxotere.

To a solution of taxotere (200 mg) in toluene (100 ml), 1,8-(diazabicyclo) [5.4.0] undec-7-ene (4 mg) was added and the whole was stirred at reflux for 8 hours. The solution was diluted with ethyl acetate, the organic layer was washed with diluted HCl, water and brine. Drying and evaporation was followed by silica chromatography (ethyl acetate:hexane) to afford 140 mg of the title compound.

1H - NMR ($CDCl_3$) δ: 3.6 (m, 1H, 7β).

Example 31

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-alanyl-2'-taxol.

A solution of β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid disodium salt)))-alanyl-2'-taxol in water-ethanol 9:1, was chromatographed on an Amberlite IR-120 (H) column, with water-ethanol 9:1 as eluant.
The solution was evaporated in vacuum to dryness, affording the title compound.

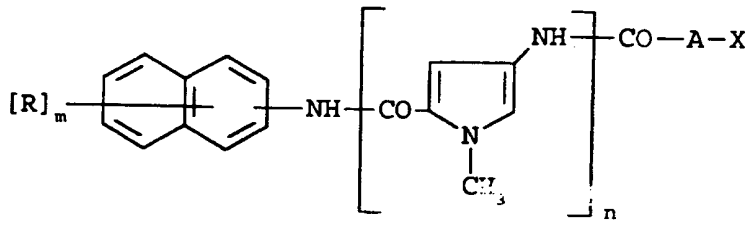
Example 32

Intravenous infusion 1-10 mg/ml.

An intravenous infusion pharmaceutical preparation can be manufactured by dissolving 500 mg of compound FCE 28284 in water for injection (100 ml).
Prior to infusion, the obtained solution can be diluted according to the common practice, and stored and/or delivered in glass, polypropylene, polyolefin or polyethylene-lined equipment.
By proceeding analogously, an intravenous infusion pharmaceutical preparation containing 1-10 mg/ml of compound FCE 29142 or compound FCE 28855 can be manufactured.

CLAIMS

1. A compound of formula (II)



(II)

wherein

R is an acidic group;

m is an integer of 1 to 3;

n is zero or an integer of 1 to 3;

A is an enzymatically hydrolyzable spacer;

X is a biologically active compound; and the pharmaceutically acceptable salts thereof.

2. A compound of formula (II), according to claim 1, wherein R is an acid group chosen from a sulfonic, carboxylic and phosphonic acidic group.

3. A compound of formula (II), according to claim 1, wherein X is a compound selected from a taxane compound, distamycin compound, a ceramide compound, a camptothecin compound, an epipodophyllotoxin compound, an anthracycline compound, benzoyl-carbinol, tetrahydro S and hydrocortisone.

4. A compound of formula (II), according to claim 1, wherein the enzymatically hydrolyzable spacer A is:

a) a group -Y-CO-, wherein Y is a C_1-C_6 alkylene or C_2-C_6 alkenylene chain, a bivalent C_3-C_5 cycloalkyl or phenylene group; or

b) an amino acid residue or a peptide spacer selected from βAla, Gly, Phe-Gly, Phe-Phe-, Leu-Gly, Val-Ala, Phe-Ala, Leu-Phe, Leu-Ala, Phe-Leu-Gly, Phe-Phe-Leu, Leu-Leu-Gly, Phe-Tyr-Ala, Phe-Gly-Phe, Phe-Phe-Gly, Phe-Leu-Gly-Phe, Gly-Phe-Leu-Gly-Phe, Gly-βAla, Phe-Gly-βAla, Phe-Phe-βAla, Leu-Gly-βAla, Val-Ala-βAla, Phe-Ala-βAla, Leu-Phe-βAla, Leu-Gly-βAla, Phe-Leu-Gly-βAla, Phe-Phe-Leu-βAla, Leu-Leu-Gly-βAla, Phe-Tyr-Ala-βAla, Phe-Gly-Phe, Phe-Phe-Gly-βAla, Phe-Leu-Gly-Phe-βAla, Gly-Phe-Leu-Gly-Phe-βAla and aminocaproyl.

5. A compound of formula (II), according to claim 1, wherein

R is a sulfonic acid group;

m is 2 or 3;

n is 1 or 2;

A is a group -Y'-CO-, wherein Y' is selected from $-CH_2-CH_2-$, -CH=CH-, and a cyclopropyl or 1,2-phenylene group; or an aminoacid residue or peptide spacer selected from β-Ala, Gly, Leu-Gly and Phe-Leu-Gly;

X is a compound selected from taxol, 7-epitaxol, epirubicin, taxotere, camptothecin, 9-amino-camptothecin, etoposide, doxorubicin, methoxy-morpholino-doxorubicin, benzoylcarbinol, tallimustine-amidoxime, a N-(C_2-C_{30})-acyl-D-sphingosine, tetrahydro S and hydrocortisone, and the pharmaceutically acceptable salts thereof.

6. A compound selected from:

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic

acid)))-β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-2'(7-epi)taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-2'(7-epi)taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-2'-taxotere;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-2'-taxotere;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-3'-etoposide;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-β-alanyl-3'-etoposide;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-β-alanyl-3'-doxorubicin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-

naphthalentrisulfonic acid))-β-alanyl-3'-doxorubicin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid))-β-alanyl-21-tetrahydro S;

N-(4-carbonylamino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))-β-alanyl-21-hydrocortisone;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid))-propionyl-2'-taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid))-propionyl-2'-taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))-propionyl-2'-taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid))-propionyl-2'-(7 epi)taxol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))-propionyl-2'-(7 epi)taxol

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid))-propionyl-2'-taxotere;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))-propionyl-2'-taxotere;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic

acid)))-propionyl-20-camptothecin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))-propionyl-20-(9-amino) camptothecin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-propionyl-3'-etoposide;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-propionyl-14-(3'-methoxymorpholino)-doxorubicin;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid)))-propionyl-1-benzoyl carbinol;

β-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid)))-propionyl-21-hydrocortisone;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino-1,7-naphthalendisulfonic acid))β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(7-imino-1,3,5-naphthalentrisulfonic acid))β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))β-alanyl-2'-taxol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl-2'-taxol;

3-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl-2-pyrrolecarbonyl-(7-imino-1,3-naphthalendisulfonic acid)))propionyl-3'-N-daunorubicin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-

methyl,2-pyrrolecarbonyl-(4-imino,1,7-naphthaledisulfonic acid))-β-alanyl-20-O-camptothecin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(4-imino,N-methyl,2-pyrrolecarbonyl-(4-imino,1,7-naphthaledisulfonic acid))-phenylalanyl-leucyl-glycyl-20-O-camptothecin;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl-O-benzoylcarbinol;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl-β-alanyl-O-benzoylcarbinol;

21-(N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl)hydrocortisone;

N-(4-carbonylimino,N-methyl,2-pyrrolecarbonyl-(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl)-O-tallimustine amidoxime;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-acetylamido-4-octadecene;

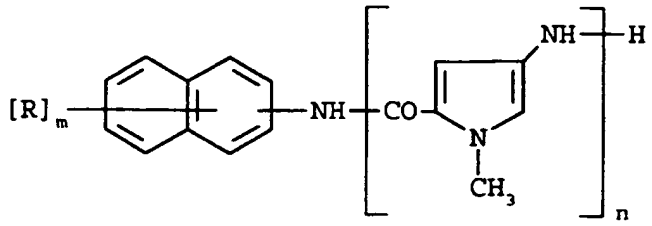
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-exanoylamido-4-octadecene;

1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))phenylalanyl-

leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene;
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene;
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-acetylamido-4-octadecene;
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-exanoylamido-4-octadecene;
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(7-imino-1,3-naphthalendisulfonic acid))β-alanyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene;
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene; and
1-O-(N-(4-carbonylimino,N-methyl-2-pyrrolecarbonyl(8-imino-1,3,5-naphthalentrisulfonic acid))phenylalanyl-leucyl-glycyl)-(2S,3R,4E)-1,3-dihydroxy-2-octadecanoylamido-4-octadecene;
or a pharmaceutically acceptable salt thereof, in particular a sodium salt.

7. A process for the preparation of a compound of formula (II), as defined in claim 1, or a salt thereof, the process comprising

a) reacting a compound of formula (III)



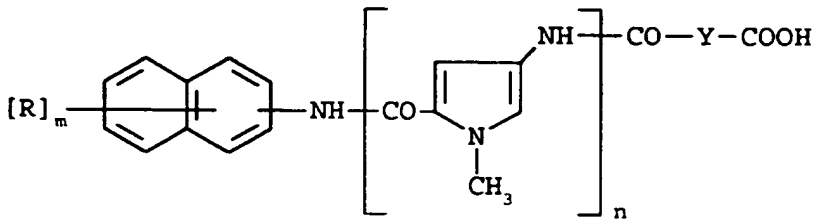
(III)

wherein R, m and n are as defined in claim 1, with a compound of formula (IV)

X-CO-Y-COOH (IV)

wherein X is as defined in claim 1 and Y is a C_1-C_6 alkylene or C_2-C_6 alkenylene chain, a bivalent C_3-C_5 cycloalkyl or phenylene group, thus obtaining a compound of formula (II) wherein A is a group -Y-CO-; or

b) reacting a compound of formula (V) or a reactive derivative thereof



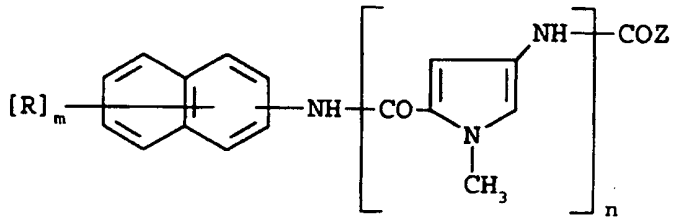
(V)

wherein R, m and n are as defined in claim 1 and Y is as defined above, with a compound of formula (VI)

X (VI)

wherein X is as defined in claim 1, thus obtaining a compound of formula (II) wherein A is a group -Y-CO-; or

c) reacting a compound of formula (VII)



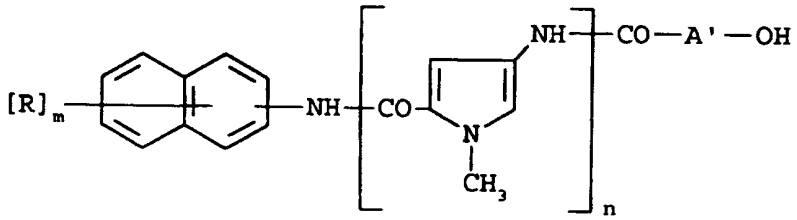
(VII)

wherein R, m and n are as defined in claim 1 and Z is a leaving group, with a compound of formula (VIII)

X-A'H (VIII)

wherein X is as defined in claim 1 and A' is as A an aminoacid residue or a peptidic spacer as defined in claim 4, thus obtaining a compound of formula (II), wherein A is an aminoacid residue or a peptide spacer; or

d) reacting a compound of formula (IX)



(IX)

wherein R, m and n are as defined in claim 1 and A' is as A an aminoacid residue or a peptidic spacer as defined in claim 4, or a reactive derivative thereof, with a compound of formula (VI)

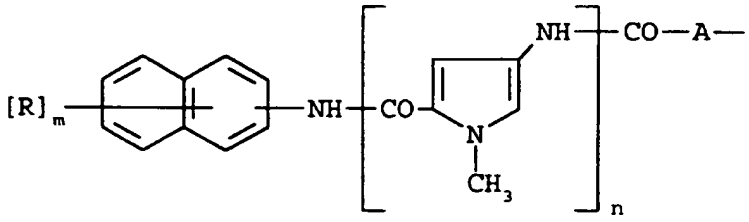
X (VI)

as defined in claim 1, thus obtaining a compound of formula (II), wherein A is an aminoacid residue or a peptide spacer; and, if desired, salifying a compound of formula (II); and/or, if desired, making free a compound of formula (II) from a salt thereof; and/or, if desired, separating an isomer of a compound of formula (II) from a mixture thereof.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, at least a compound of formula (II), as defined in claim 1, or a pharmaceutically acceptable salt thereof.

9. A compound of formula (II), or a pharmaceutically acceptable salt thereof, as defined in claim 1, for use as an antiproliferative, in particular anti-tumor and anti-angiogenic agent, and as an anti-inflammatory agent.

10. A process for improving systemic bioavailability of a biologically active compound X, the method comprising providing such active compound X bound to a carrier group



(I)

wherein

R, m, n and A are as defined in claim 1;

or a pharmaceutically acceptable salt thereof.

11. A process according to claim 10 wherein the compound X is a compound selected from a taxane compound, a distamycin compound, a ceramide compound, a camptothecin compound, an epipodophyllotoxin compound, an anthracycline compound, benzoylcarbinol, tetrahydro S and hydrocortisone; or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 96/00528

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H15/252 C07K5/06 C07K5/08 C07K5/10 C07K7/06
C07D207/34 C07D405/12 C07D405/14 C07D491/22 A61K31/40
A61K31/57 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H C07K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO,A,95 23806 (PHARMACIA S.P.A., ITALY) 8 September 1995 see the whole document	1-11
A	ANTIVIRAL RES. (1995), 27(4), 335-54 CODEN: ARSRDR;ISSN: 0166-3542, 1995, XP002004932 CLANTON, DAVID J. ET AL: "Novel sulfonated and phosphonated analogs of distamycin which inhibit the replication of HIV" see the whole document	1-11

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 June 1996	14.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Kissler, B

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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